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ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,652	LIBUTTI ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments to the claims filed on May 25, 2007 have been received and entered. Claim 41 has been amended.

Election/Restrictions

Applicant's election with traverse of the invention of claims 1-20 (group I) filed October 4, 2006 was acknowledged. The traversal was on the grounds that Examiner has not set forth convincing argument that the search and examination of all the groups necessarily represents an undue burden for the examiner. Applicant's argument for examining remaining claims drawn to a method of measuring the angiogenic activity of a test molecule by comparing the fluorescence vascular density were persuasive since both sets of group embrace methods of measuring angiogenic or anti angiogenic activity. Therefore, invention of claims 26-40 (group I) directed to a method of measuring angiogenic activity by comparing the fluorescence vascular density assay is rejoined with elected inventions of group II for the examination purposes. Applicants have also elected polypeptide, synthetic molecule, fluorescein, XTT, serum and filter paper as species for claims readable on claims 26-50.

Claims 26-50 are currently under consideration.

Priority

It was noted that instant application is a 371 of PCT/US03/10932 filed on 04/09/2003 which claims benefit of 60/371,010 filed on 04/09/2002. However, upon review the disclosure of the prior-filed application, US provisional application 60/371,010, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. It is noted that 60/371,010 dated 4/9/2002 describes measuring angiogenic activity using fluorescence vascular density but does not show support for a method to determine angiogenic activity using XTT. Consequently, there is no written description in

application for using XTT or any other metabolic agent to determine angiogenic activity using spectrophotometer. In case, if applicants have evidence to support otherwise, applicants are invited to indicate page and line number for the written support as recited in claims 41-50 of the instant application. Therefore, the effective filing date for instant claims 41-50 is 04/09/2003 as subject matter of instant claims was described in the 60/371,010.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 26-50 rejected under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant arguments. Examiner would agree that those skilled in the art routinely use fluorescent particle and other metabolic agent or substrate to analyze biological process as argued by the applicants and therefore these would require routine experimentation, which would not be undue experimentation for one of skill in the art.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 26-27, 29-41 and 43-50 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn. Examiner would agree that specification reasonably convey to an artisan that applicants had possession of the claimed invention at the time of filing of this application.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 37-40 and 41-50 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. The rejection to claims 17-20 for not further limiting the method of claim 1 is withdrawn as steps set forth in claim 17-20 are not required to practice independent claim. Examiner would also agree that the term "lower spectrophotometer absorbance and higher spectrophotometer absorbance in

claim 21 and relative fluorescent brightness " in claim 19 is not a relative term and therefore these claims are not indefinite. Although specification does not define these term but exemplify method to calculate relative fluorescent brightness.

Withdrawn- Claim Rejections - 35 USC § 103

Claims 26-40 rejected under 35 U.S.C. 103(a) as being unpatentable over Brooks et al; (Methods in Molecular Biology, 129, 257-269, IDS), Kurz et al (Developmental Dynamics, 1995, 203, 174-186), Frasca et al (Oncogene, 2001: 20, 3845-3856) and Kinnman et al (Lab Invest. 2001; 81(12): 1709-16) is withdrawn. Examiner has inadvertently included claims 26-40 in the rejection. It is noted that the method disclosed by combination of references are obvious to a method of measuring angiogenesis by comparing the absorbance of test region using metabolic agents and not using a fluorescent labeled particle as recited in claims 26-40.

Maintained- Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26-34, 36-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brooks et al; (Science, 1994, 264, 570-571 IDS) and Robert et al (Cancer Res. 1992; 52(4): 924-30) and Kimel et al (SPIE, 1996, 2628, 69-76, IDS).

Brooks et al teach a method to measure angiogenic and anti angiogenic activity of a test molecule by obtaining a 10 day old chick egg wherein it is candled to determine prominent blood vessel and then via a small window of exposed area a filter disc is placed followed by systemic administration of test molecule (see pages 570, Figure 2 A and B). It is noted that Brooks et al also suggest filter disc saturated with teat agent which could be angiogenic stimulator that could be placed on the CAM (see page 570, Figure 2A, 3). Brooks et al also teach quantitation of angiogenic or anti angiogenic activity by removing the filter disc and associated CAM tissue that is snap frozen and sections that are stained with different antibody for staining of vessel which is analyzed using confocal microscopy (see page 570, Figure 2 A and B). Brooks et al analyzed average rhodamine fluorescence for each vessel per unit area to measure laser confocal image to determine angiogenic or anti angiogenic activity. While Brooks et al described the potential of measuring angiogenic and anti angiogenic activity using CAM assay and also disclosed quantified relative expression of integrins during bFGF induced angiogenesis by laser confocal image analysis (see Figure 3, page 571). Brooks et al differed from the claimed invention by not teaching administering fluorescent-labeled particle before removing the test region of interest and capturing the 3D image of the test region to quantitate angiogenesis in the test area.

However, prior to instant invention was made, Robert et al teach a method using chick embryo wherein different photo sensitizer including photofrin, cyanine and uroporphyrin were administered by different method including direct injection of photo sensitizer into the vessel to compare photo sensitizer uptake/retention in proliferating and non proliferating neovasculature (see abstract and page 925, col. 1, para. 4). The fluorescence is calculated using spectrofluorimeter to analyze photo sensitizer content (see page 925, col. 1, extraction). Robert et al provide evidence that photo sensitizers are preferentially retained by tumors have a selective affinity for proliferating neovasculature. It is noted that Robert et al disclose that the chloroaluminum sulfonated phthalocyanine and tetraphenyl porphine sulfonate compounds possess the greatest affinity for proliferating neovasculature relative to nonvascular tissue (see abstract and Figure 2 and 3). This is further supported by studies conducted by Kimel et al that taught an *in vivo* uptake of porphyrin using CAM model to document fluorescence in real time at different time interval to demonstrate bio distribution of porphyrin (see abstract and conclusion).

Robert differed from the claimed invention by not teaching administering an anti angiogenic agent and measuring the fluorescence by confocal to measure the angiogenic or anti angiogenic activity. However, the use of confocal microscope for measuring the angiogenic activity was known in the art at the time the claimed invention was made and these were routinely used as evidenced by Brooks et al (supra).

Accordingly, in view of the teachings of Brooks and Robert, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method to measure angiogenic or anti angiogenic activity in a CAM assay of Brooks by measuring fluorescent vascular density taught by Robert/ Kimel with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Robert had already disclosed that

phthalocyanine and tetraphenyl porphine sulfonate compounds possess the greatest affinity for proliferating neo vasculature relative to non vascular tissue (supra) and particularly since both Brooks and Kimel et al sought to quantitate retention of fluorescent moiety in CAM. Although Brooks et al did not adminster the fluorescent moiety before removing the substrate; he generally embraced potential of measuring fluorescence for quantification to better measure and compare angiogenesis. In addition, Robert et al and Kimel provided motivation of using porphyrin or cyanine to measure the bio distribution in neo vasculature in CAM assay (supra). Therefore, given that many methods to measure fluorescence including FACS and confocal microscopy (as per the teaching of Brooks and Kimel) during morphogenesis were available to compare the angiogenic activity it would have obvious for an artisan to adminster porphyrin or cyanine directly into the vessel as taught by Robert/Kimel and determine fluorescence using the method of Brooks/Kimel to measure angiogenic or anti angiogenic activity as disclosed in the instant application. It is noted that the skilled Artisan would have further motivated to optimize the treatment routes, regimen and would have optimized the steps of administering test molecule in different vessel depending upon total volume of test agent required for the angiogenic or anti angiogenic response as per the teachings of Brooks (see MPEP 2144.04).

One who would practiced the invention would have had reasonable expectation of success because Brooks had already taught a method to measure angiogenic or anti angiogenic agent activity in a CAM assay. Robert et al and Kimel et al had described use of porphyrin or cyanine to measure the bio distribution in neo vasculature in CAM, which could have been used as for quantitation to compare angiogenic or anti angiogenic activity. Thus, it would have only required routine experimentation to modify the method disclosed by Brooks and Robert to include steps of administering porphyrin or cyanine directly to vessel and measure angiogenic or anti angiogenic activity as required by instant invention.

It is noted that claims 37-40 are included in the rejection because these are method steps are inherently present in order to determine fluorescence using confocal microscope as required by claim 26 (see 112 paragraph 2).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 26-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brooks et al; (Science, 1994, 264, 570-571 IDS) and Rizzo et al (Microvascular Res, 1995, 49, 49-63, IDS).

The teachings of Brooks has been discussed above and relied in same manner here. However, Brooks et al do not explicitly teach administering FITC labeled particle to measure angiogenic activity.

Rizzo et al taught a method to quantitate the relative micro vascular permeability associated with tumorigenesis and normal angiogenesis by microinjecting a graded series of FITC-dextrans into a vessel of CAM and then measuring the fluorescence by a confocal attachment to differentiate different capillary network (see page 50 bridging to

page 51; materials and method). The results of Rizzo et al provide evidence that CAM could be sued as an attractive model to investigate the vasculature (see page 62, last two lines). Rizzo et al differed from the claimed invention by not teaching administering an angiogenic agent and measuring the fluorescence by confocal to measure the angiogenic or anti angiogenic activity. However, the use of confocal microscope for measuring the angiogenic activity was known in the art at the time the claimed invention was made and these were routinely used as evidenced by Brooks et al (supra).

Accordingly, in view of the teachings of Brooks and Rizzo, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method to measure angiogenic or anti angiogenic activity in a CAM assay of Brooks by measuring fluorescent vascular density taught by Rizzo with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Robert had already disclosed that FITC-dextran could be microinjected to determine the vasculature (supra) and particularly since both Brooks and Rizzo et al sought to quantitate fluorescence in vasculature. Although Brooks et al did not adminster the fluorescent moiety before removing the substrate; he generally embraced potential of measuring fluorescence for quantification to better measure and compare angiogenesis. In addition, Rizzo provided motivation of using FITC-dextran to measure the neo vasculature in CAM assay because permeability of 10-day-old embryo may relect functional adaptation of the CAM (abstract). Therefore, given that many methods to measure fluorescence including confocal microscopy were available as per the teachings of Brooks amd Rizzo, it would have obvious for an artisan to adminster FITC-dextran directly into the vessel as taught by Rizzo and determine fluorescence using the method of Brooks/Rizzo to measure angiogenic or anti angiogenic activity as disclosed in the instant application. It is noted that the skilled Artisan would have further motivated to optimize the treatment routes, regimen and would have optimize the steps of administering test molecule in different vessel depending upon total volume of test agent required for the angiogenic or anti angiogenic response as per the teachings of Brooks (see MPEP 2144.04).

One who would practiced the invention would have had reasonable expectation of success because Brooks had already taught a method to measure angiogenic or anti angiogenic agent activity in a CAM assay. Rizzo et al had already described use of FITC-dextran to measure the bio distribution in neo vasculature in CAM that could have been used as for quantitation to compare angiogenic or anti angiogenic activity. Thus, it would have only required routine experimentation to modify the method disclosed by Brooks and Rizzo to include steps of administering FITC-dextran directly to vessel and measure angiogenic or anti angiogenic activity as required by instant invention.

It is noted that claims 17-20 are included in the rejection because these are method steps are inherently present in order to determine fluorescence using confocal microscope as required by claim 1 (see 112 paragraph 2).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 41-50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brooks et al; (Methods in Molecular Biology, 129, 257-269, IDS), Kurz et al (Developmental Dynamics, 1995, 203, 174-186), Frasca et al (Oncogene, 2001: 20, 3845-3856) and Kinnman et al (Lab Invest. 2001; 81(12): 1709-16).

Brooks et al teach a method to measure angiogenic and anti angiogenic activity of a test molecule by obtaining a 10 day old chick egg wherein it is candled to determine prominent blood vessel and then via a small window of exposed area a filter disc is placed followed by systemic administration of test molecule (see Figure 1pages 261-264). It is noted that Brooks et al also suggest filter disc saturated with teat agent which could be angiogenic stimulator could be placed on the CAM (see Figure 1 page 263). Brooks et al also indicate that only up to 100□l of single injection could be administered to the vessel (see page 264, paragraph 1). Brooks et al also teach quantitation of angiogenic or anti angiogenic activity by removing the filter disc and associated CAM tissue that is placed on petri dish for quantitation of number of blood vessels (see page 265, paragraph 1). While Brooks et al described the potential of measuring angiogenic and anti angiogenic activity using CAM assay. Brooks et al differed from the claimed invention by not teaching use of adding an agent to measure metabolic activity to quantitate number of viable cells in the test area.

However, prior to instant invention was made, use of proliferation-based assays was routine in the art to quantitate angiogenic or anti angiogenic activity. Kurz et al taught a method to analyze the density and distribution of whole mount BrdU anti BdU labeled endothelial cell in a CAM with computer assisted microscopy. It is noted that Kurz et al taught a method to obtain CAM at different days (see page 175, col. 2, para. 3) that were analyzed for the influence of VEGF in proliferation intensity. Kurz et al also described the nuclear incorporation (metabolic degradation) of BrdU is not as rapid in avian cells (see page 182, col. 1, para. 1, and Figure 5). It is emphasized that Kurz et al proposed that CAM endothelial proliferation is regulated by a factor such as endothelial cell density of pre capillary vessel and length density of pre-capillary vessel, which should be used for evaluation of angiogenesis in the CAM assay (see abstract).

Kurz differed from the claimed invention by not teaching administering an agent XTT and measuring the metabolic activity to measure the metabolic activity of cell in the test area. However, the uses for XTT, MTT, WST-1or BrdU for measuring the cell proliferation was known in the art at the time the claimed invention was made and these assay were routinely used in alternative to each other.

Frasca et al taught a method of determining the effect of a synthetic molecule STI571 on HGF-induced morphogenesis. It is noted that Frasca taught a method to determine the proliferation of cells on matrigel to determine the effect of test agent on proliferation during morphogenesis. Frasca et al describe addition of an agent XTT after the addition of test molecule and described the method to measure and compare the metabolic activity at a specific wavelength (450nm) as described by the manufacturer (Roche Laboratory see page 3855, col. 1, para. 3, and Fig. 3). In addition, Kinnman provided evidence that cell proliferation/ cell viability could be measured by multiple

method including BrDu, XTT and cell counting (see page 1711, Figure 5). However, Frasca et al do not explicitly teach a method of comparing proliferation of cells during the formation of capillary in a CAM assay.

Accordingly, in view of the teachings of Brooks and Kurz, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method to measure angiogenic or anti angiogenic activity in a CAM assay of Brooks by measuring endothelial cell density with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Kurz had already disclosed that proliferative pattern and the length density and extension should be used for the evaluation of angiogenesis in the CAM (see page 174, abstract, last 5 lines) and particularly since both Kunz and Brooks et al sought to quantitate angiogenic or anti angiogenic activity. Although Brooks or Kurz et al did not use XTT, Kurz generally embraced potential of measuring proliferation assay to better measure and compare angiogenesis. In addition, Kurz provided motivation of measuring proliferation of cells to measure the vessel density and length for quantitation of angiogenesis in CAM assay (supra). Therefore, given that many methods to measure proliferation of cell including XTT, Brdu were available for determining the proliferation of cells during morphogenesis to compare the angiogenic activity of test molecule as per the teachings of Frasca and Kinnman it would have obvious for an artisan to use XTT or any other assay to determine cell viability/proliferation assay or metabolic activity to measure angiogenic or anti angiogenic activity as disclosed in the instant application. It is noted that the skilled Artisan would have further motivated to optimize the treatment routes, regimen and would have optimize the steps of administering test molecule and agent to measure metabolic activity in different vessel depending upon total volume of test agent required for the angiogenic or anti angiogenic response as per the teachings of Brooks (see MPEP 2144.04).

One who would practiced the invention would have had reasonable expectation of success because Brooks had already a method to measure angiogenic or anti angiogenic agent activity in a Cam assay. Kurz and Frasca had already described use of proliferation/viability assay to determine proliferation pattern during morphogenesis that could have been used as for quantitation to compare angiogenic or anti angiogenic activity. Thus, it would have only required routine experimentation to modify the method disclosed by Brooks and Kurz to include XTT assay to measure angiogenic or anti angiogenic activity as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Brooks et al, Robert et al and Kimel

Applicant's arguments filed on May 25, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument point out that the claimed methods are screening method that allows identification of compounds. Applicants assert that Brooks, Kimel et al or Roberts et al., either alone nor in combination disclose or suggest a screening method to identify compounds with angiogenic or anti angiogenic activity.

In response it is noted that claim 1 is directed to a method of measuring angiogenic or anti angiogenic activity comprising (a) obtaining an fowl egg, (b) creating a window in the shell of the egg, (c) providing to a test region of interest on the CAM a substrate; (d) administering to a vessel located in the CAM a test molecule, (e) administering to a vessel located in the CAM a fluorescent-labeled -particle, such that the fluorescent-labeled particle travels through each vessel contained in the test region of interest, (f) removing the substrate and the test region of interest from the fowl egg, (g) capturing a three-dimensional image of the test region of interest, and (h) comparing the FVD value of the test region of interest with the FVD value of a control region with the administration of a control molecule.

It appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention of a screening method. It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole.

It is noted that independent claim 1 is open-ended and therefore may include additional method steps. Contrary to applicant's argument, Brooks et al teach a method comprising measuring the test agent (bFGF) as compared to untreated control by (a) obtaining a 10 day old chick egg, (ii) creating a candled to determine prominent blood vessel and then (ii) via a small window of exposed area a filter disc is placed (iii) followed by administering systemic administration of test molecule (see pages 570,

Figure 2 A and B). Brooks et al also suggest filter disc saturated with teat agent which could be angiogenic stimulator that could be placed on the CAM (see page 570, Figure 2A, 3). Brooks et al also teach quantitation by removing the filter disc and associated CAM tissue that is snap frozen and sections by staining of vessel that is analyzed using confocal microscopy. It is noted that specification defines test agent may include any protein, polypeptide, or peptide (See page 11, para. 33 of the specification) which would classify bFGF as test agent. It is emphasized that based on the definition set forth in the specification bFGF could be considered as test agent. Furthermore, one of ordinary skill in the art could easily substitute other structurally equivalent known or unknown agent as a test agent. One skilled in the art would be aware of such structurally and functionally equivalent substitute to practice the method steps disclosed by Brooks. In fact, another reference of Brooks (Methods in Molecular Biology, 129, 257-269, IDS) cited by the Examiner for other 103 rejections uses same method and discloses systemic administration of test molecule in general term. In the instant case, Brooks (Science, 1994, 264, 570-571 IDS) teach systemic administration of test molecule (bFGF).

Next applicant argues that the cited reference of Brooks discloses amount of integrin expression during angiogenesis and not the angiogenic activity. In response, it is noted that it is generally known in the art that angiogenesis is characterized by invasion, migration and proliferation of smooth muscle and endothelial cell (see Brooks et al page 569, col. 2, last para). Brooks et al also concluded both chicken and human vessels have higher $\alpha v\beta 3$ expression (see page 570, col. 1, last para). Thus, contrary to applicants argument method disclosed by Brooks also embrace comparing extent of angiogenesis by determining the relative fluorescence of integrin in test (bFGF) and control group (see page 570, Figure 2 A and B). Brooks et al analyzed average rhodamine fluorescence for each vessel per unit area to measure laser confocal image to determine angiogenic or anti angiogenic activity.

Applicant also argues that there is no suggestion of a compound and fluorescent labeled particle that have been administered to a vessel that travel through each vessel contained in the test region with a reasonable expectation of success.

In response, it is emphasized that if Brooks had disclosed systemic administration of a fluorescent molecule for determining the angiogenesis then this would have been an anticipation rejection and not obviousness type rejection. Examiner has clearly stated that while Brooks et al described the potential of measuring angiogenic and anti angiogenic activity using CAM assay and also disclosed quantified relative expression of integrins during bFGF induced angiogenesis by laser confocal image analysis (see Figure 3, page 571). Brooks et al differed from the claimed invention by not teaching administering fluorescent-labeled particle to a vessel before removing the test region of interest and capturing the 3D image of the test region to quantitate angiogenesis in the test area. However, at the time of filing of instant invention, fluorescent-labeled particles were routinely used for imaging vasculature as evident by secondary references of Robert et al and Kimel.

With respect to applicants argument that there is nothing in Brooks that would motivate the administration of a fluorescent molecule (see page 21, para. 1 of the argument), it is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant case, references of Robert and Kimel provided adequate guidance with respect to other known techniques that would have been obvious to one of ordinary skill in the art to combine with method of Brooks in order to improve the method to measure extent of fluorescence in real time with reasonable degree of predictability.

Applicant's argument with respect to Robert and Kimel (pages 21-22 of the argument) not teaching screening method, it is emphasized that contrary to applicant's

argument these references are not included to demonstrate method to screen test agent for angiogenesis. In fact these references are included to demonstrate that prior to instant application, it was generally known that phthalocyanine and tetraphenyl porphine sulfonate compounds possess the greatest affinity for proliferating neo vasculature relative to non vascular tissue (see Robert, supra), while Kimel et al sought to quantitate retention of fluorescent moiety in CAM using fluorescence in real time at different time interval to demonstrate bio distribution of porphyrin. Brooks et al did not adminster the fluorescent moiety before removing the substrate; he generally embraced potential of measuring fluorescence for quantification to better measure and compare angiogenesis. Robert et al and Kimel provided adequate guidance of using porphyrin or cyanine or any other known or unknown fluorescent particle to measure the bio distribution in neo vasculature using CAM assay (supra). Therefore, given that many methods to measure fluorescence including FACS and confocal microscopy (as per the teaching of Brooks and Kimel) during morphogenesis were available to compare the vasculature (angiogenic activity), it would have been *prima facie* obvious to one of ordinary skill in the art to apply the techniques of Robert and Kimel to determine the fluorescence in the vessels of CAM region in order to improve the fluorescence detection method in all the vessel of CAM using the technique disclosed by Brooks et al with reasonable expectation of success.

With respect to applicants argument that consistency and stability of fluorescence are crucial to the step of removing a test agent and there is no reasonable expectation to achieve stable fluoresce. In response, it is noted that Kimel exemplified a real time detection and quantitation to measure different porphyrins products (see page 70 material and method). It is noted that Kimel provided guidance with respect to temporal distribution of sensitizer uptake in a CAM model using a real time monitoring of *in vivo* fluorescence. It is noted that independent claim 26 does not require any specific fluorescent-labeled particle, while dependent claim 36-lists number of fluorescent-labeled particle including GFP, cyanine and rhodamine based compounds. In the instant case, Brooks, Robert and Kimel provided adequate guidance with respect to availability of different fluorescent-labeled particle including rhodamine and other cyanine based

compounds. Furthermore, applicants in his arguments agree that many of the fluorescent-labeled particles are commercially available and they are routinely used for analyzing biological processes (see page 10 and 11 of the applicant's argument). One of ordinary skill in the art would have known other commonly used or unknown fluorescent labeled particle suitable for the instant purpose that are stable and prevents photo bleaching with reasonable degree of predictability (see page 11, last para. of the argument and page 12, line 11-12).

Brooks and Rizzo

Applicant's arguments filed on May 25, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument point out that Rizzo et al related to a method of studying micro vascular permeability during normal angiogenesis. Applicants assert that art focused on the use of known molecule to study the physiological response and there is no suggestion of doing any screening assay. Applicants argue that, the experimental approach used by Rizzo et al differs significantly from the claimed method as no test molecule is administered and Rizzo et al. is merely studying the permeability of a fluorescent molecule during angiogenesis. No angiogenic effect attributable to any compound is being measured. In the methods of the present invention, the test molecule and the fluorescent-labeled particle are administered to a test region in the CAM inside the shell. Nothing in Rizzo et al. would lead one of skill in the art to believe that a test molecule and FITC-dextran can be administered to a vessel in a test region of the CAM of a live embryo and that this test region can subsequently be removed for image capturing and quantitative analysis of angiogenic or anti angiogenic activity (see page 22 of the argument, para. 2).

In response, it is reiterated that instant rejection is not anticipation rejection rather it is obviousness type rejection. It appears that applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In

re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988). The reference of Rizzo et al is included to demonstrate that microinjecting a fluorescent labeled particle such as FITC-dextrans into a vessel of CAM and subsequently measuring the fluorescence by a confocal to differentiate different capillary network was known in prior art. It is noted that applicant's argument that method disclosed by Rizzo did not teach test molecule and the fluorescent-labeled particle are administered to a test region of the CAM inside the shell. In response, it is noted that Brooks et al had disclosed a method to adminster test agent in the CAM inside the shell, while Rizzo provided guidance with respect to feasibility of administering FITC-dextran in a cultured CAM. It is emphasized that teaching of Rizzo is not to disclosed method steps for administering test agent rather it is used to show that method of administering fluorescent particle directly to vessel for detection of microvasculature was known in prior art. Although, Rizzo et al disclose injecting FITC-dextran in a shell less CAM, however, given that method of administering agent in CAM inside shell was also known as per the teaching of Brooks, it would have been prima facie obvious to one of ordinary skill in the art to inject fluorescent labeled particle in the vessel of CAM in the shell or without the shell with reasonable expectation of success. The reference of Rizzo teaches administering FITC-dextran to the vessel of CAM changes in the interstitial optical intensity due to FITC-dextran extravasations (see abstract). Furthermore, the results of Rizzo et al provide evidence that CAM could be used as an attractive model to investigate the microvasculature (see page 62, last two lines). Examiner would agree that Rizzo did not explicitly teach a method to screen any agent, but provided adequate guidance with respect to systemic administration of fluorescent-labeled particle for the purpose of studying microvasculature. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to apply the technique of administering FITC-dextran in vessel of CAM with or without shell to improve the detection method disclosed by Brooks to measure extent of angiogenesis. Brooks had already disclosed feasibility of administering test agent in blood vessel of CAM inside a

shell in order to improve the method with a predictable results to screen angiogenic agent by combining the standard CAM assay with a fluorescent detection method disclosed by Rizzo to determine the fluorescence in presence and absence of test agent.

Brooks et al (Methods in Molecular Biology, 1999); Kurz, Frasca; Kinnman

As an initial matter it is noted that applicants have not argued or rebutted the teachings of Brooks et al (Methods in Molecular Biology, 1999) that was cited by the Examiner, which is different from Brooks et al (Science, 1994). Therefore, rejection to claims 41-50 is maintained for the reason of record. It is noted that in absence of any argument presented against the primary reference any subsequent argument to only secondary reference is not a complete response, hence, instant response to applicant's argument is directed to the extent they address the specific issues raised by the secondary reference.

Applicant's arguments filed on May 25, 2007 have been fully considered but they are not fully persuasive because instant response fails to completely address the rejection of record.

Applicants point out that Kurz is directed to the measurement of proliferation in the cultured (not intact) CAM. There is no teaching or suggestion in Kurz et al. of utilizing a metabolic agent to assess angiogenic or antiangiogenic activity of a test molecule. Applicants assert that the lack of teaching regarding screening makes this paper lack motivation to screen the activity of unknown compounds. Applicants argue that Kurz et al merely provides an alternative method of measuring proliferation that is carried out utilizing cultured CAMs not CAMs in an eggshell as required by the present methods. Applicants also argue that there is no indication in Kurz et al. that BrdU can be administered to a vessel in a test region of the CAM, while still in the shell, such that the test region can subsequently be removed in order to measure proliferation. Thus, there is no reasonable expectation of success that a

combination of Kurz et al. can be combined with Brooks et al. or Frasca et al. to produce a useful result. Applicants also assert that Frasca et al. describe the addition of XTT after the addition of a test molecule and described a method of measuring and comparing the metabolic activity at a specific wavelength, but this is not applied in the context of angiogenesis. Rather, it relates to the measurement of metabolic activity in cell proliferation that has no bearing on, and is, thus, not suggestive of the measurement of angiogenic or anti-angiogenic activity in a test region of the CAM after administration of a test molecule and a metabolic agent *in vivo*. Applicants assert that there would be no motivation or any reasonable expectation of success that Brooks et al. in combination with any of Kurz et al., Frasca et al. and Kinnman et al. would allow one of skill in the art to arrive at the present invention.

It appears that Applicant is arguing that the cited references do not expressly suggest or provide motivation for using metabolic agent for measuring the angiogenic activity. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole. In the instant case, Examiner has provided the reference of Brooks et al (1999) that teaches a method to measure angiogenic and anti angiogenic activity of a test molecule by obtaining a 10 day old chick egg wherein it is candled to determine prominent blood vessel and then via a small window of exposed area a filter disc is placed followed by systemic administration of test molecule (see Figure 1pages 261-264). It is noted that Brooks et al also suggest filter disc saturated with teat agent which could be angiogenic stimulator could be placed on the CAM (see Figure 1 page 263). Brooks et al also indicate that only up to 100μl of single injection could be administered to the vessel (see page 264, paragraph 1). Brooks et al also teach quantitation of angiogenic or anti angiogenic activity by removing the filter disc and associated CAM tissue that is placed

on petri dish for quantitation of number of blood vessels (see page 265, paragraph 1). While Brooks et al described the potential of measuring angiogenic and anti angiogenic activity using CAM assay. Brooks et al differed from the claimed invention by not teaching use of adding an agent to measure metabolic activity to quantitate number of viable cells in the test area. It is emphasized that prior to instant invention is was generally known to one of ordinary skill in the art that angiogenesis involves proliferation of endothelial cell which is also evident from the teaching of Kurz et al that discloses that CAM endothelial cell proliferation is regulated by endothelial cell density and extension and these proliferation should be used for the evaluation of angiogenesis in CAM assay (see abstract). With respect to applicant's argument that there is no motivation to combine any of the reference, it is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988).

In the instant case, prior to instant invention, use of proliferation-based assays was routine in the art to quantitate proliferation of endothelial cells. Applicants agree that Kurz provides an alternative method of measuring proliferation that is carried out utilizing cultured CAMs. Although, Kurz exemplified a method that differed from the claimed invention by not teaching administering an agent XTT or any other metabolic agent for measuring the metabolic activity in the test area. However, uses of XTT, MTT, WST-1or BrdU for measuring the cell proliferation was known to one of ordinary skill in the art at the time the claimed invention was made and these assay were routinely used in alternative to each other as evidenced by the teaching of Frasca and Kinnman.

Although Brooks or Kurz et al did not use XTT, Kurz generally embraced potential of measuring proliferation assay to better measure and compare angiogenesis. In addition, Kurz provided adequate guidance for measuring proliferation of cells to measure the vessel density and length for quantitation of angiogenesis in CAM assay (supra). Therefore, given that many methods to measure proliferation of cell including XTT, MTT and Brdu were commercially available for determining the proliferation of EC during morphogenesis to compare it would have *prima facie* obvious to one of ordinary skill in the art to use any metabolic agent to determine cell viability/proliferation to measure density of endothelial cells as an index of angiogenic activity in the method of Brooks with reasonable expectation of success to compare the metabolic activity of test agent to untreated control as a measure of relative angiogenic activity.

Maintained- Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 26-50 remains provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-2, 7-22 and 27-35 of copending Application No. 11/014472. It is noted that both sets of claims are directed to a method of measuring the angiogenic or anti angiogenic activity of a test molecule in a CAM assay by administering a fluorescent-labeled particle and measuring the FVD value or by using

an agent that has metabolic activity and measure spectrophotometer reading to determine angiogenic activity. Since the specification and claims of the '472, application contemplated same test molecule and fluorescent-labeled particle or by using XTT and embraced same method steps in CAM assay as one disclosed in instant application.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

It is noted that applicants have indicated that instant rejection would be addressed once claims are found allowable in either application.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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